PERIPHERAL VASOCONSTRICTION BY TOBACCO AND ITS RELATION TO THROMBO-ANGIITIS OBLITERANS

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From clinical observations, very definite opinions have been expressed concerning the relationship of tobacco to thrombo-angiitis obliterans:

Erb,[1] in 1904, concluded that tobacco smoking was a definite contributing factor to the production of peripheral vascular deficiences. Buerger[2] assigns tobacco smoking as a predisposing cause of thrombo-angiitis obliterans and states that it is possible that the use of tobacco may render the vessels more susceptible to special agents, toxic or infectious, but that tobacco is the only cause or the exciting cause is exceedingly doubtful. Brown, Allen and Mahorner[3] agree with Buerger. Willy Meyer[4] presents tobacco-smoke poisoning as the one etiological factor responsible for the characteristic syndrome of thrombo-angiitis obliterans. Silbert,[5] in reviewing 289 cases of this disease, is convinced that smoking is the most important contributing factor in producing the disease and that cessation of smoking is an essential therapeutic measure. He stated that 50 per cent. of the patients requiring amputation continued to smoke in spite of repeated warnings and that recurrence of symptoms after the individual had been restored to good condition was almost invariably traceable to a resumption of smoking. In only two of Silbert's cases had a progression of the disease taken place when the patient was not using tobacco. Samuels[6] insists that the first point in the treatment of thrombo-angiitis obliterans is the absolute prohibition of the use of tobacco.

The study by Barker[7] of the tobacco usage at the onset of the symptoms, not that used after severe pain or gangrene, in 350 cases of thrombo-angiitis obliterans, shows conclusively that a greater percentage (87 per cent.) of the individuals with that disease use tobacco than do other groups; that they smoke cigarettes much more (91.5 per cent.) than other forms of tobacco; that as a group they consume more tobacco than other individuals and finally, that the severity of their disease is greater in the excessive users than that in the very few non-users and mild users of tobacco.

A considerable amount of experimental work has been done with tobacco and its derivatives. In the literature we have found only three investigations[8,9,10] demonstrating the peripheral vasoconstrictor effect of tobacco smoking in man. We have seen no reference to these articles in discussions of the possible relationship of tobacco smoking to thrombo-angiitis obliterans. Recently, in a preliminary report,[11] we presented definite evidence of the peripheral vasoconstrictor action of tobacco smoking in man by means of skin-temperature changes. We wish here to report this work in detail.

Normal subjects.—The investigation was carried on in a small room in which the temperature could be controlled at a fairly constant level, the range being from 25.0° to 28.0° C.* A small electric fan running at low

* In order to show an increase in peripheral vasoconstriction it was not desirable to have the normal peripheral vasconstriction at its maximum at the onset of the experiment. Accordingly, fairly warm room temperatures were used, under which condition peripheral vasoconstriction is at a low degree or may be entirely lacking.

speed provided a circulation of air. No talking was allowed and every effort was made to eliminate psychic factors. The subject, lying quietly on a bed and wearing shorts in the case of the men and shorts and a breast covering in the case of the women, was exposed to the environmental conditions for one hour.* At five-minute intervals blood-pressure and pulse readings were then made on the right arm and skin-temperature measurements were taken with a "Tycos Dermatherm" on the palmar tips of the left fingers and the plantar tips of the left toes.† On some subjects the skin temperature just above the umbilicus and of the right toes was recorded. After a fairly constant skin-temperature level had been reached the subject was given his customary form of tobacco to smoke at his usual rate. Following completion of the smoking the patient continued to lie quietly in order to determine

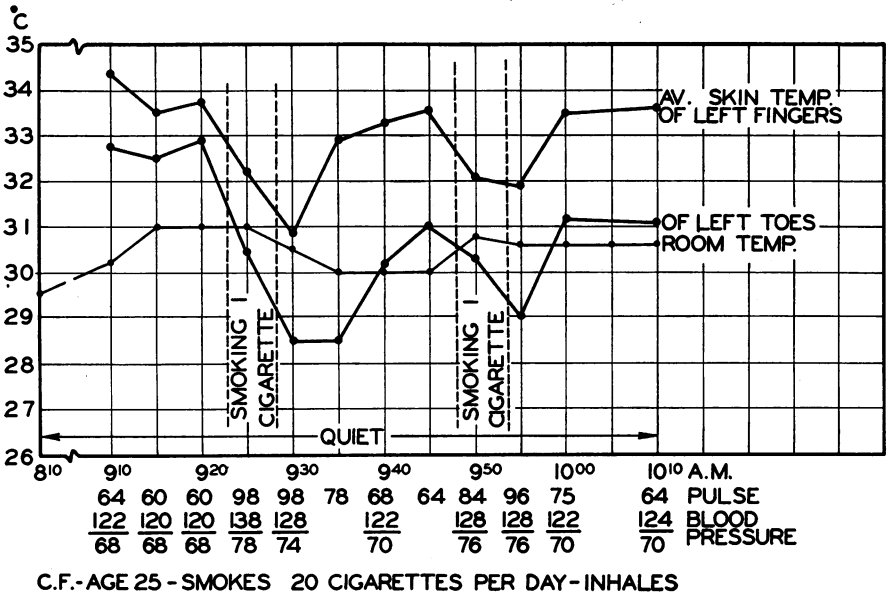

FIG. 1.—The effect of cigarette smoking on blood-pressure, pulse rate and peripheral skin temperature.

whether the cardiovascular changes that resulted during the smoking period would return to their previous levels. The experiment was carried out with twenty subjects between twenty and thirty years of age, the majority of whom were medical students. Both light and heavy smokers were included in the group.

Under the conditions of the study the data obtained from subject C. F. and shown in Fig. 1 demonstrated that with smoking there occurred an increase in blood-pressure and pulse rate and a decrease in the skin temperature of the left fingers and toes. On cessation of smoking the first cigarette,

*This initial period was selected in order to allow for an adaptation of the skin temperature to the environmental temperature.

† These measurements were taken routinely on the one side only because it has been repeatedly shown[12, 18] that normally the skin temperature of symmetrical body points is approximately the same.

TABLE I

Blood-Pressure, Pulse Rate and Skin-Temperature Changes with Tobacco

Subject	1 H.S.	2 C.F.	3 C.H.	4 S.B.	5 C.F.	6 H.J.	7 R.H.	8 C.H.	9 M.F.	10 H.B.	11 M.B.
Age	18	26	23	24	25	25	28	23	29	30	23
Sex	F.	M.	M.	M.	M.	M.	M.	M.	M.	M.	M.
Average smoking per day											
Cigarettes	20	20	12	20	18	15	20	12	35		15
Pipefuls										6	
Inhales smoke	+	+	+	+	+	+	+	+	+	−	−
Smoked during test—cigarettes or pipefuls	1	1	2	2	2	3	3	3	2	2	4
Time smoking—minutes	7	5	20	20	14	25	15	25	12	44	25
On smoking											
Increase in systolic B.P. in mm. of Hg	20	18	8	20	16	18	10	10	18	8	10
Increase in diastolic B.P. in mm. of Hg	14	10	25	10	6	16	0	20	10	10	4
Increase in pulse rate per minute	8	38	20	20	34	18	18	16	26	24	12
Decrease in av. skin temp. left fingers in °C.	4.5	2.8	3.0	1.5	2.5	2.2	3.5	6.0	4.5	3.0	0.7
Decrease in av. skin temp. left toes in °C.	2.5	4.5	1.0	3.0	4.0	4.5	0.5	2.0	4.3	2.5	1.6
Time required in minutes to return to level previous to smoking											
Systolic B.P.	20	12	14	15	10	15	15	12	10	20	4
Diastolic B.P.	20	12	20	6	10	15	15	12	10	30	2
Pulse rate	20	15	20	5	15	5	15	12	10	30	4
Skin temperature, fingers	5	15	70	20	45	35	20	60	10	40	10
Number of degrees C. of the temperature of the toes below their pre-smoking level at the time the temperature of the fingers had returned to their original level	1.5	1.8	0.0	1.5	1.0	2.0	0.0	1.0	3.5	2.5	0.5

the blood-pressure and pulse rates returned to their previous level in approximately twelve minutes; the skin temperatures of the fingers increased to their previous level in seventeen minutes, while at that time the toes were still 2.0° C. below their original temperature. The same response occurred on smoking a second cigarette. The nineteen other subjects in this group on smoking showed the same changes to a greater or less degree as the example presented. The data from eleven of them are given in Table I. Occasionally a subject noted mild vertigo and nausea on smoking. This was stated to be no greater than often experienced in their usual smoking habits. There were no significant changes in mouth temperature and skin temperature about the waist during an experiment. The magnitude of the changes

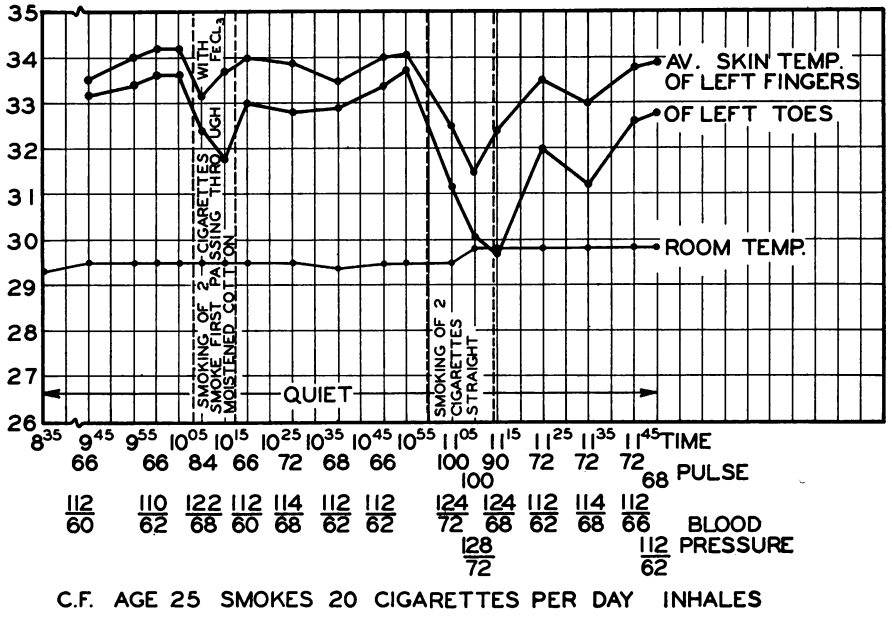

FIG. 2.—A lessened cardiovascular response as a result of the smoke first passing through a filter.

in blood-pressure, pulse rate and peripheral skin temperature was greater with rapid smoking than with slow smoking and again with "inhaling" the smoke than with merely "puffing." (Subject 11, Table I.)

Subject 9 of Table I, an Austrian Jew, smoked thirty-five to forty cigarettes per day. In spite of this habitual excessive use of tobacco there was a marked cardiovascular response to the smoking of two cigarettes. In subject 10 of Table I the usual changes recorded on cigarette smoking were noted from pipe smoking.

The possibility was raised that some other factor than tobacco smoke was responsible for the result obtained. Accordingly, a series of control experiments was made. These consisted of changing the original conditions of the smoking experiment as follows: First, the substitution of cubebs for cigarettes, and second, by having the subject go through the motions of

smoking with a small paper tube or an empty pipe. With these substitutions there were negligible changes in blood-pressure, pulse rate and peripheral skin temperature. In the third group of controls the smoke was first passed through two water bottles or through a layer of cotton moistened with $FeCl_3$,[9] thereby removing some of its components. A decreased cardiovascular response resulted, an example being shown in Fig. 2.

The data from these control experiments substantiated our opinion that the increase in blood-pressure and pulse rate and the decrease in peripheral skin temperature found on smoking were due to active products absorbed from the tobacco smoke. This conclusion is in entire accord with the work of Simici and Marcu.[9]

The decrease in the peripheral skin temperature of our young adult group on smoking was of particular interest to us. This effect must be due to increased peripheral vasoconstriction. From a contemplation of this fact, several questions arose. We did not attempt to enumerate nor to answer all of them in this study. Of special interest appeared:

(1) Through what mechanism does tobacco smoking produce peripheral vasoconstriction in man?

(2) What components or component of the tobacco smoke is responsible for this action?

In 1908, Lee[14] presented the composition of tobacco smoke obtained by an aspirator from the slow combustion of 100 grams of tobacco as follows:

Nicotine, 1.165 grams. This represented 50 per cent. of the total nicotine present before combustion. Pyridine bases, 0.146 gram, chiefly pyridine and collodine, the former being produced during the destruction of some of the nicotine, the latter from the combustion of the fibres in the tobacco. Hydrocyanic acid, 0.08 gram; ammonia, 0.36 gram; carbon monoxide, 410 cubic centimetres.

Many ingenious animal experiments support the view that the site of action of a tobacco infusion[15] and of nicotine lies in the vasomotor nervous system. Langley and Dickinson[16] proved that nicotine stimulates sympathetic ganglion cells. Hoskins and Ransom[17] consider the pressor effect of nicotine due about one-half to a stimulation of the vasoconstrictor centre proper in the medulla and one-half to a stimulation of the sympathetic ganglion cells.

A few variations in our original smoking procedure presented data in man in accord with these conclusions. The decrease in the skin temperature of the toes shown on smoking was approximately the same for both feet. On two normal subjects a block of the left posterior tibial nerve with 2 per cent. procaine was done at the tip of the medial malleolus. This procedure interrupted the nerve supply to the plantar surface of the left toes. The usual smoking experiment was then started and both subjects showed the same result. On smoking a decrease occurred in the skin temperature of the right toes but did not occur in the left toes where the nerve was blocked.

It was evident, then, that the peripheral vasoconstriction produced by tobacco smoking in these two normal subjects was brought about through the nerve mechanism and was not a direct effect on the musculature of the vessel walls.

This phase of our investigation was furthered by the opportunity to do the smoking experiment on an individual who had had a cervicodorsal ramusectomy and ganglionectomy and a lumbar ganglionectomy for Raynaud's disease. The sympathetic nervous system control to the extremities of this individual was abolished by this procedure. On smoking, the usual blood-pressure and pulse increase were found but no change occurred in the peripheral skin temperature. With this fact in view, we proceeded one step further from the conclusion reached as a result of the nerve-block experiment and considered that the peripheral vasoconstriction produced by tobacco smoking was brought about through the sympathetic nervous system.

Nicotine.—From animal experimentation Lee[14] concludes that nicotine is the most important poison in tobacco. Cushny[18] considers it to be the only constituent of tobacco possessing any toxicological interest. Sollmann[19] states that the effects of tobacco are due practically solely to its nicotine content and that nicotine is absorbed extremely rapidly from the mucous membranes and especially from the lungs. We were interested then in determining whether nicotine administered by other channels would produce the same effect on blood-pressure, pulse rate and peripheral skin temperature as that shown by our young adults when smoking cigarettes.

A recent study[20] reported the average nicotine content of four popular brands of cigarettes to be 2.2 per cent. Since there is approximately one gram of tobacco in each of these cigarettes, there is an average of twenty-two milligrams of nicotine present.

Several investigators have undertaken the problem of the nicotine content of tobacco smoke and the amount absorbed on smoking.[21,22] Baumberger,[23] from his study, concludes that an average of 0.573 per cent. of the weight of cigarette tobacco appears as nicotine in the smoke. Applying this figure along with the consideration that about two-thirds of a cigarette is smoked shows 1.0 by .66 by 0.573 = 3.78 milligrams of nicotine appearing in the smoke of a cigarette. From a further study Baumberger[24] concludes that 66.7 per cent. of the smoke of tobacco is retained in the subject on puffing, and 88.2 per cent. on inhaling. He assumes that it is undoubtedly true that nicotine and total smoke would be retained in the same proportion and that therefore 66.7 per cent. of the nicotine would be absorbed in puffing and 88.2 per cent. on inhaling. Applying these figures the nicotine theoretically absorbed from the smoking of two-thirds of one cigarette on puffing would be 66.7 per cent. of 3.78 milligrams = 2.52 milligrams and by inhaling 88.2 per cent. of 3.78 milligrams = 3.33 milligrams.

Nicotine has been given in small amounts by mouth[25] without untoward symptoms. Absorption from the respiratory tract is definitely a more direct route to the general circulation than from the gastro-intestinal canal. With the question of the rate of absorption from the stomach and upper intestines there is also the claim that there is some destruction or detoxification of nicotine in the liver.[26] An intravenous administration to the general circulation more closely approximates the respiratory-tract absorption.

Under the conditions of the smoking experiment a total of six milligrams of nicotine hydrochloride was given by mouth at the rate of one milligram in thirty cubic centimetres of water at ten-minute intervals to

two young adult smokers and one non-smoker. Other than a mild irritative effect in the mouth and pharynx there were no symptoms. The blood-pressure, pulse and skin-temperature changes noted on smoking did not occur. We were convinced that minute quantities of nicotine could be given intravenously to smokers with safety. Solutions were prepared containing 0.1 milligram of nicotine tartrate or the alkaloid in one cubic centimetre of physiological saline. In order to obviate the psychic factor responsible for the momentary peripheral vasoconstriction incident to the puncturing of the vein for intravenous medication, a two-way valve was added

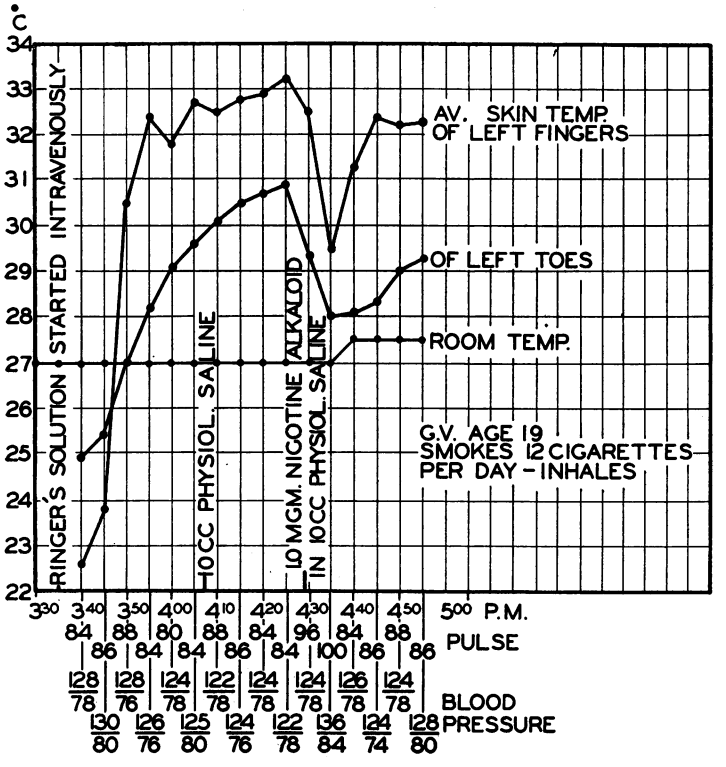

FIG. 3.—The effect of a 1.0 milligram of nicotine given intravenously on blood-pressure, pulse rate and peripheral skin temperature.

to the needle attachment of the burette used for the administration of intravenous fluids. Under our standard conditions Ringer's solution was then given intravenously in the left arm at the rate of 150 to 200 cubic centimetres per hour. As the subject became accustomed to the procedure the peripheral skin temperature rose to a fairly constant level. The valve was then turned and as a control ten cubic centimetres of physiological saline were slowly injected. The Ringer's solution was continued for a few minutes and then the nicotine was injected and followed by Ringer's solution to the end of the experiment. The data obtained from subject G. V. (Fig. 3), show that on the intravenous injection of one milligram of nicotine there occurred an

increase in blood-pressure and pulse rate and a decrease in the skin temperature of the fingers and toes. As in the case of subjects smoking, the effect of the nicotine on the peripheral skin temperature was of longer duration than the effect on the pulse rate and the blood-pressure. Also, the skin temperature of the toes showed a slower rise towards their previous level than the case with the fingers. In Table II the results obtained with the four subjects of this study are presented.

TABLE II

Nicotine Intravenously

Subject	F.B.	H.G.	G.V.	H.L.
Age	33	18	19	45
	C.	C.	C.	P.
Average smoking per day, cigarettes or pipefuls	10	20	12	15
Total nicotine tartrate or alkaloid administered in mgms.	6	3	1.5	5
Increase in systolic B.P. in mm. of Hg	16	14	12	12
Increase in diastolic B.P. in mm. of Hg	4	2	6	4
Increase in pulse rate per minute	8	36	16	8
Decrease in av. skin temp., fingers °C	4.5	3.5	3.5	2.0
Decrease in av. skin temp., toes °C	1.5	0.5	2.7	1.2
Increase in rate and depth of resp. with each administration of nicotine	+	+	+	+
Mild aching in left arm	0	+	+	0
Mild vertigo	0	+	0	+
Peculiar taste in mouth	0	+	+	0

The nicotine administered intravenously was not greater than that theoretically absorbed from the smoking of two cigarettes. The data obtained show blood-pressure, pulse rate and skin-temperature changes fairly analogous with those of the normal subjects of Table I. This would tend to bear out in man the contention of Lee, Cushny, Sollmann and others that the effects of tobacco are due practically to its nicotine content.

Thrombo-angiitis Obliterans.—The application of this investigation to patients with thrombo-angiitis obliterans was carried out with considerable interest.

In Fig. 4 is shown the result of our study on F. S., aged fifty years, whose symptoms began fifteen years previously with intermittent claudication of both legs. He stated that from 1924 to 1929 he had smoked about ten cigarettes and two cigars a day. His general course had been periods of remissions and exacerbations of the intermittent claudications, always worse in the left leg, and with occasional periods of rest pain. No ulcerations or gangrene had developed. General physical examination was essentially normal, excepting the lower extremities. Both legs and feet showed some atrophy of the soft tissues. There was pallor of the feet on elevation and rubor on dependency, both being more marked on the left. Lower extremity pulses were:

	Right leg	*Left leg*
Popliteal artery	Fair	Slight
Posterior tibial artery	Fair	Slight
Dorsalis pedis artery	Fair	Slight

As a result of smoking under the same conditions used for the normal subjects this patient showed a marked decrease in the skin temperature of the toes and an increase

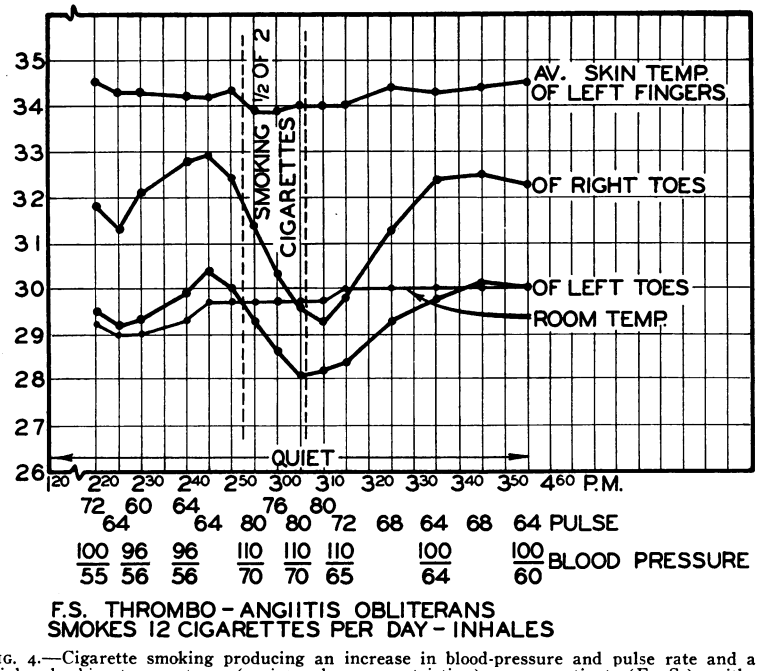

FIG. 4.—Cigarette smoking producing an increase in blood-pressure and pulse rate and a decrease in peripheral skin temperature (peripheral vasoconstriction) in a patient (F. S.) with thrombo-angiitis obliterans.

in blood-pressure and pulse rate. Remembering that clinically the vascular deficiency was greater in the left foot than in the right, we found it to be in accord that the skin

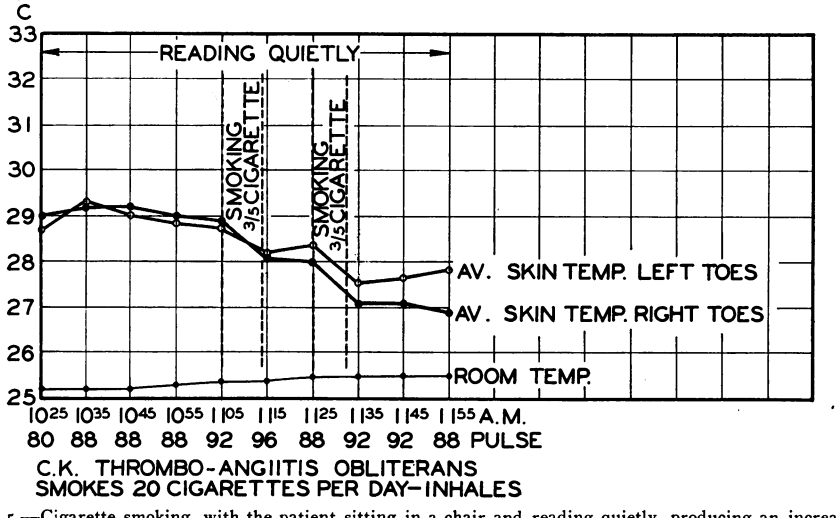

FIG. 5.—Cigarette smoking, with the patient sitting in a chair and reading quietly, producing an increase in pulse rate and a decrease in peripheral skin temperature (peripheral vasoconstriction).

temperature of the left toes throughout the experiment was lower than that of the right. Also considering that there were probably fewer uninvolved branches of the vascular

bed in the left foot capable of constricting, it was reasonable that, on smoking, the decrease in the skin temperature of the left toes, of approximately 2.4° C., was less than that of the right toes of 3.5° C. From the onset of smoking the skin temperatures of the toes did not return to their previous level for approximately forty-five minutes. Comparatively, there was a much greater response in the toes of this individual over the fingers than was observed in the normal subjects. Interestingly, it was noted that although this man tried to minimize his tobacco consumption by stating that he smoked only half of each cigarette we have never seen a subject inhale the smoke as deeply as in his case.

With a second case of thrombo-angiitis obliterans, C. K., the study was carried out under slightly different circumstances. Clinically, the extent of the vascular impairment in each leg was about equal. The patient wearing flannel pajamas sat in a comfortable chair with his legs resting on a low stool. His feet were uncovered. At the beginning of the experiment he started to read a magazine article and was told to smoke when and as he desired. Quietly, skin temperature measurements of the toes were recorded and pulse counts were taken from the right wrist. In Fig. 5 are shown the decreased peripheral skin temperatures and increased pulse rate incident to smoking.

Comment.—This study made on the effect of tobacco smoking, largely in the form of cigarettes, on young adult smokers, demonstrated a consistent increase in blood-pressure and pulse rate and a decrease in the skin temperature of the fingers and toes. Control experiments gave definite evidence that these effects were due to active products absorbed from the tobacco smoke. Nicotine administered intravenously in quantities not greater than that theoretically absorbed in the smoking of one or two cigarettes produced comparatively analogous changes. Greater effects were noted when the subject "inhaled" while smoking rather than merely "puffing," and also with rapid smoking more than with slow smoking.

The decrease in the peripheral skin temperature on smoking must be due to increased vasoconstriction. In a previous article[13] we pointed out the value of measurements of the skin temperature of the fingers and toes under well-controlled conditions as indications of stimulation or depression of the sympathetic nervous system. In this study the decrease in the peripheral skin temperature was shown to be carried out through that system. While the peripheral vasoconstriction on smoking was usually measured only in the fingers and toes, the points of maximal response to changes in peripheral vasomotor tonus,[13] it is undoubtedly true that vasoconstriction of skin vessels occurred to a lesser degree over the entire body.

By increasing peripheral vasoconstriction smoking reduced the blood supply of the fingers and toes of the young adults studied. With several subjects the reduction lasted more than thirty minutes from the time of cessation of smoking and generally was of longer duration in the toes than in the fingers. In the two cases of thrombo-angiitis obliterans cited, smoking produced the same cardiovascular response as in the normal subjects. The already deficient circulation in the feet of these two patients was further reduced by smoking, the decrease in F. S. (Fig. 4) lasting forty-five minutes.

We do not offer the data presented by this investigation as evidence that tobacco smoking is the etiological factor in thrombo-angiitis obliterans. The

occurrence of the disease in individuals who have never smoked precludes that opinion. It is interesting, however, to recall that other vasoconstricting substances, pituitrin[27] and particularly ergot, have been responsible for peripheral vascular occlusions and gangrene. Recently Kaunitz[28] pointed out the pathological similarity of thrombo-angiitis obliterans and endemic ergotism. In regard to marked vasospasm of neurogenical origin, Spurling, Jelsma and Rogers[29] demonstrated organic vascular changes in the fingers of a patient with long-standing Raynaud's disease. We have no doubt but that prolonged or marked vasoconstriction for a sufficient period of time may initiate organic vascular occlusions. The changes may occur not only in peripheral arterioles, capillaries and venules but also in peripheral arteries and veins as a result of zones of poor nutrition in their walls through vasoconstriction of their vasa-vasorum.

The criterion of a satisfactory result in the treatment of thrombo-angiitis obliterans is the avoidance of amputations and the return of the individual to his occupation. Every effort towards that ideal is based on the principle of increasing the peripheral circulation. The demonstrated vasoconstrictor effect of tobacco smoking would lessen or nullify the benefits of all conservative treatment. The experimental data presented form a rational basis for the clinical conclusions as to the deleterious influence of tobacco smoking on the progress of thrombo-angiitis obliterans. Its use definitely further decreases the already deficient circulation in the extremities of the individuals with that disease. We unhesitatingly counsel against tobacco smoking by patients with thrombo-angiitis obliterans.

BIBLIOGRAPHY

[1] Erb, W.: Ueber Dysphasia Angiosclerotica. Munchen. med. Wchnschr., vol. 51, pp. 905–908, 1904.

[2] Buerger, Leo: The Circulating Disturbances of the Extremities. W. B. Saunders and Co., Phiadelphia, 1924.

[3] Brown, Allen, and Mahorner: Thrombo-angiitis Obliterans. Mayo Clinic Monographs, 1928.

[4] Meyer, Willy: The Etiology of Thrombo-angiitis Obliterans. Med. Rec., vol. xcv, p. 901, 1919.

[5] Silbert, Samuel: Thrombo-angiitis Obliterans. Jour. Am. Med. Assn., vol. xciv, p. 1730, May 31, 1930.

[6] Samuels, S.: The Treatment of Gangrene Due to Thrombo-Angiitis Obliterans. Jour. Am. Med. Assn., vol. xcvi, p. 751, March 7, 1931.

[7] Barker, N. W.: The Tobacco Factor in Thrombo-Angiitis Obliterans. Proc. Mayo Clinic, vol. vi, February 4, 1931.

[8] Bruce, James W., Miller, James R., and Hooker, Donald R.: Am. Jour. of Physiol., vol. xxiv, p. 104, 1909.

[9] Simici, D., and Marcu, Q.: Recherches Plethysmographiques sur l'Action Vasculare de la Fumee de Tabac chez l'Homme. J. de Physiol. et de Path. Generale, vol. xxv, p. 57, 1927.

[10] Ralli, Elaine P., and Oppenheimer, B. S.: Changes in the Peripheral Circulation Accompanying "Tobacco Angina." Proc. Soc. Exp. Biol. and Med., vol. xxvi, pp. 9–11, 1928.

[11] Maddock, Walter G., and Coller, Frederick A.: Peripheral Vasoconstriction by Tobacco Demonstrated by Skin-temperature Changes. Proc. Soc. Exp. Biol. and Med., vol. xxix, pp. 487–488, 1932.

[12] Benedict, Francis G., Coropatchinsky, V., and Finn, M.D.: Measurement of the Skin Temperature of Humans. Jour. de Physiol. et de Pathol. Gen., 1928b, Amerika-Band, Halle Academy of Science (in English), vol. xxv, p. 1, 1928A.

[13] Coller, Frederick A., and Maddock, Walter G.: An Environmental Test for the Differentiation of Spastic from Organic Peripheral Vascular Occlusion. (Read before American Surgical Association, New Haven, May, 1932.)

[14] Lee, Emerson: The Action of Tobacco Smoke, with Special Reference to Arterial Pressure and Degeneration. Quart. Jour. Exp. Physiol., vol. i, p. 35, 1908.

[15] Saccheto, I., and Martinelli, L.: Azione del Fuma di Tabacco Sul Sistema Nervosa Vasomotore. Cuore e Circulazione, vol. xi, p. 276, 1927.

[16] Langley, J. N., and Dickinson, W. H.: Pituri and Nicotin. Jour. Physiol., vol. xi, p. 297, Cambridge, 1890.

[17] Hoskins, R. G., and Ransom, W. S.: The Vasomotor Reaction to Nicotine Locus of Stimulation. Jour. of Pharm. and Exp. Therap., vol. vii, p. 375, 1915.

[18] Cushny, Arthur R.: Pharmacology and Therapeutics. Philadelphia, p. 308, 1918.

[19] Sollmann, Torald: A Manual of Pharmacology. Philadelphia, 1927, p. 406.

[20] Consumers Research Handbook of Buying, Fourth Revision, October, 1930.

[21] Lehman, K. B.: Vorlaufige Mitteilungen uber Tabakstudien. Hyg. Rundschau., vol. xvii, p. 1100, 1907.

[22] Asherton, N.: Nicotine. Chem. News, vol. cxx, p. 150, 1919.

[23] Baumberger, J. P.: The Nicotine Content of Tobacco Smoke. Jour. of Pharm. and Exp. Therap., vols. xxi–xxii, p. 35, 1923–1924.

[24] Baumberger, J. P.: The Amount of Smoke Produced from Tobacco and Its Absorption in Smoking as Determined by Electrical Precipitation. Jour. of Pharm. and Exp. Therap., vol. xxi–xxii, p. 47, 1923–1924.

[25] Lehmann, K. B.: Untersuchungen über das Tabakrauchen. Munchen. med. Wchnschr., p. 723, 1908.

[26] Dixon, W. E., and Lee, W. E.: Tolerance to Nicotine. Quart. Jour. Exp. Physiol., vol. v, p. 372, 1912.

[27] Holsclaw, F. M., and Booth, J. A.: Symmetrical Gangrene Following Excessive Dose of Pituitrin. Arch. Pediat., vol. xlii, p. 64, 1925.

[28] Kaunitz, Julius: The Pathological Similarity of Thrombo-angiitis Obliterans and Endemic Ergotism. Am. Jour. of Path., vol. vi, p. 299, 1930.

[29] Spurling, Glen R., Jelsma, Franklin, and Rogers, James B.: Observations in Raynaud's Disease. Surg., Gynec. and Obst., vol. liv, p. 584, March, 1932.